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Decoding the Connection: Cervicovaginal Microbiome, HPV, and Cervical Cancer

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ABSTRACT

In low- and middle-income countries (LMICs), where access to screenings and preventative care is restricted, cervical cancer continues to pose a serious threat to world health. In these areas, it is the third most prevalent cancer among women, and increased incidence and mortality are a result of resource inequities. The human papillomavirus (HPV), a sexually transmitted infection, is the main cause of cervical cancer. Nonetheless, studies reveal a complex interplay among environmental, genetic, and epigenetic factors, with mounting evidence supporting the role of the cervicovaginal microbiome. This microbial community controls vaginal health and modulates HPV risks, with some bacterial species, such as those linked to bacterial vaginosis (e.g., Lactobacillus iners), potentially promoting HPV persistence and cervical dysplasia. On the other hand, beneficial species, including Lactobacillus crispatus and Lactobacillus gasseri, contribute to an acidic environment that counters inflammation and may limit HPV progression. Although progress has been made in understanding these dynamics, much remains unknown about the factors influencing microbiome variability and how to manipulate it to prevent disease. Meanwhile, established preventive measures, such as HPV vaccination, routine screenings, and early treatment of precancerous lesions, have proven effective. However, logistical and financial challenges in LMICs hinder broader implementation. To reduce the global burden, efforts must focus on affordable vaccines, integrated screening services, and increasing public awareness. Further microbiome research offers hope for innovative prevention and treatments. Addressing systemic barriers and advancing knowledge could signify meaningful steps toward eradicating cervical cancer as a public health threat worldwide.

Keywords:
Cervical Cancer;
Human Papillomavirus;
Cervicovaginal Microbiome;
Cancer Prevention;
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Introduction

Understanding Cervical Cancer

As one of the most dangerous malignancies and the primary cause of cancer-related deaths among women globally, cervical cancer (CC) remains a major public health concern. Approximately 14% of people in the US who receive treatment for pre-cervical cancer go on to receive a CC diagnosis [1].

Cervical Cancer Progression and Staging

The transformation zone of the cervix, which is prone to cellular alterations, is where CC typically starts. After that, the illness may spread to neighboring lymph nodes. Cervical smear tests can detect precancerous lesions or very early malignancies, even though early-stage CC is frequently asymptomatic. In more advanced stages, symptoms usually become more noticeable and manifest as pain (if lymph nodes are damaged) and spontaneous or contact bleeding. To classify CC, clinical staging is necessary (Fig. 1). disease in situ, or stage 0, denotes that the disease is contained to the cervix and has not progressed to other tissues [2]. IA1 represents a very early stage of CC, often only detectable under a microscope. In this stage, the invasive cancer is limited to a depth of 3 mm and a width of less than 7 mm. As the stages progress (IA2, IB1, IB2), the depth and horizontal spread of the tumour increase, with some stages also exhibiting larger, clinically apparent lesions. Stages IIA to IVA depict the tumour's advancement beyond the cervix and into surrounding structures like the vagina, parametrium, pelvic side wall, and potentially even the bladder or rectum. Stage IVB, the most advanced stage, signifies the presence of a remote metastasis [3].

The Global Impact of Cervical Cancer

Although a decade ago cervical cancer (CC) was the third most frequent cancer among women globally, it remained the leading malignancy in women in low-income countries, reflecting a much more severe public health concern [5]. This inequality persists, with CC recognized in 2018 as the fourth most common cause of cancer mortality in women worldwide [6]. The distribution of the disease is markedly uneven across different regions. According to the World Health Organization (WHO), approximately 85% of CC cases are found in less developed nations. For instance, Mexico reports some of the highest incidence rates, reaching 14.3 per 100,000 women in 2020, whereas Germany records one of the lowest, with only 2 per 100,000 women. Furthermore, a concerning trend emerges: a rise in young women diagnosed with CC. Compared to three decades ago, estimates suggest a 10–40% increase in young women battling this disease [7].

Risk Factors for Cervical Cancer

A complex interplay of factors shapes cervical cancer development. Early sexual debut, behavioural

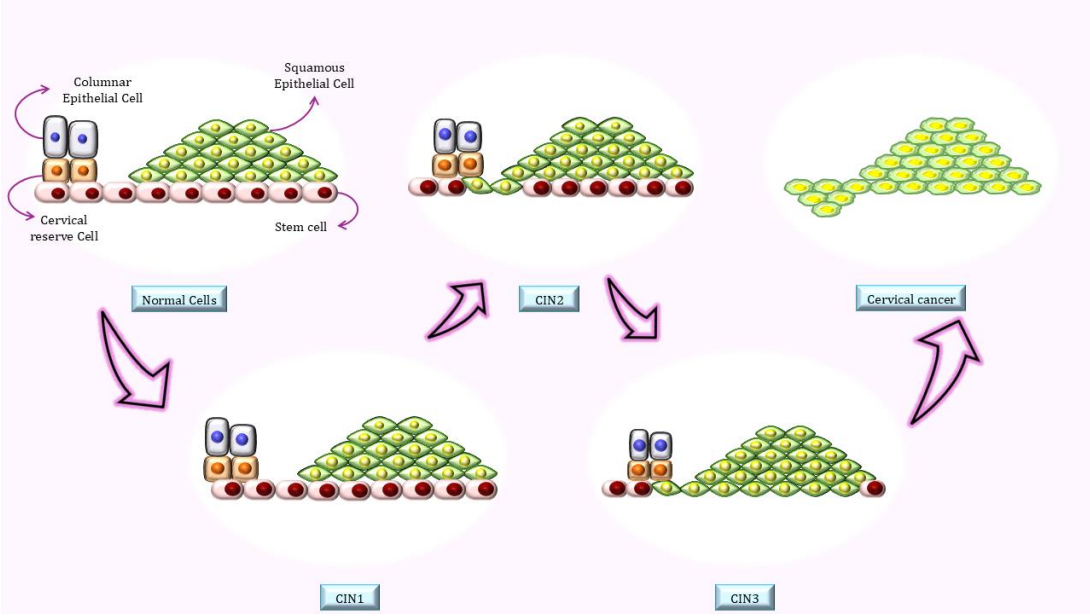


Fig. 1. hrHPV can cause CIN lesions, classified into three types: CIN1, CIN2, and CIN3. CIN3 can eventually lead to cervical cancer. In normal tissue, cells in the upper third have smaller nuclei. As tissue progresses from normal to CIN1, the size of nuclei increases, then remains stable up to CIN3. During this time, the amount of cytoplasm decreases, and differentiation increases. The upper nucleus histogram (Hst U) rises from regular to CIN1, stabilises between CIN1 and CIN2, but significantly drops from CIN2 to CIN3. Conversely, the overall nucleus histogram (Hst whole) consistently increases from normal cells to CIN3 [4].

patterns, and reproductive and sexual histories all contribute to the risk. Age, engaging in sexual activity with multiple partners, smoking, having a high number of pregnancies (high parity), and having a low socioeconomic background all appear to be risk factors [8]. A substantial body of laboratory and epidemiological research has firmly demonstrated the association between human papillomavirus (HPV) infection and the onset of cervical cancer (CC) [9, 10]. Among the various genotypes, HPV types 16, 18, 31, 33, and 45 are most commonly implicated in invasive forms of CC. Risk factors such as early initiation of sexual activity and having multiple sexual partners have been identified as increasing susceptibility to HPV infection and subsequent development of cervical malignancies [11]. Furthermore, emerging evidence suggests that the cervical microbiota may play a role in both the initiation and progression of cervical neoplasia [12]. Alterations in the composition of vaginal microbial communities may accelerate cervical cancer development, while advanced stages of the disease might, in turn, influence the structure of the vaginal microbiome [13]. These findings underscore the possible critical role of the cervicovaginal microbiota in maintaining cervical health and contributing to disease processes.

Human Papillomavirus (HPV): A Longstanding Threat with Devastating Potential

Human papillomaviruses (HPVs) are a diverse group of small, double-stranded DNA viruses that have coexisted and coevolved with the human host over thousands of years, showing relatively limited genetic diversity. While these viruses are widespread, certain high-risk types are recognized as a necessary factor in the pathogenesis of approximately 5% of all cervical cancers worldwide [14]. HPV infection represents a significant global health burden, contributing to various diseases and ranking as a leading cause of infection-related malignancies [15]. Cervical cancer (CC) stands as the most well-known example, often arising from long-term infection with specific oncogenic HPV strains. In contrast, low-risk HPV genotypes are infrequently associated with malignancy, although they can lead to benign lesions that may still cause discomfort or clinical concern in affected individuals [16].

Classification of HPV: From Harmless to High-Risk

The family Papillomaviridae consists of 29 genera, which include 189 papillomavirus types. Among these, 120 types have been identified in humans, while the remaining types have been found in animals such as non-human mammals, birds, and reptiles. Human papillomaviruses (HPVs) encompass a genetically diverse group of viruses, classified into five major genera: alpha (α), beta (β), gamma (γ), mu (μ), and nu (ν). Their classification primarily relies on the sequence of the L1 gene, which encodes the viral capsid protein [14]. Notably, the L1 gene exhibits high conservation across all known papillomaviruses and is a valuable tool for classification and phylogenetic analysis [15]. While infection with β- and γ-papillomavirus often goes unnoticed and is asymptomatic, individuals with weakened immune systems due to conditions like organ transplants, HIV infection, and epidermodysplasia verruciformis, among others, may experience increased susceptibility to cutaneous papillomas or even skin cancer from these strains. Necessarily, the alpha genus harbours genotypes implicated in cancer development [16]. With over 207 identified HPV types, of which more than 170 are fully sequenced, categorisation is based on their carcinogenic risk—low or high, particularly concerning cervical cancer [17]. Low-risk genital HPV types, such as types 6 and 11, are predominantly linked to the development of genital warts, while high-risk types are strongly associated with invasive cervical cancer (CC). Although the number of potentially high-risk HPV types ranges between 13 and 19, only 11 genotypes—namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58—are widely accepted as having significant oncogenic potential [18].

HPV Genome

The genome of human papillomavirus (HPV) maintains a conserved architecture across the Papillomaviridae family and is functionally divided into three main regions: the early coding region, the upstream regulatory region (URR), and the late coding region. The early region, designated as “E,” comprises six open reading frames (E1, E2, E4, E5, E6, and E7), which encode proteins essential for various stages of the viral life cycle and are instrumental in host cell transformation [19]. Among them, E6 and E7 are the principal oncogenes, facilitating both viral replication and adaptation to host cell environments; however, their activity may inadvertently initiate carcinogenic processes. The E1 and E2 proteins primarily contribute to viral genome replication and transcriptional regulation. The URR, a non-coding regulatory segment, contains cis-acting elements that orchestrate the transcription and replication of viral genes. Finally, the late region is responsible for encoding the structural capsid proteins, L1 and L2, which form the viral particle [20].

HPV Infection

HPV infection initiates by targeting a limited number of basal stem cells within the epithelium. In the early phase, the viral DNA replicates independently of the host cell cycle, typically reaching 50 to 100 copies per cell [21]. This initial replication is driven by the viral proteins E1 and E2, which help maintain the virus within the infected stem cells for extended periods.

As these infected cells undergo differentiation and migrate toward the epithelial surface, a regulatory shift occurs, leading to the expression of late viral genes and a dramatic increase in viral DNA replication. Meanwhile, early proteins such as E5, E6, and E7 are believed to modulate the host cellular environment to support efficient viral proliferation. This manipulation can stimulate host cell DNA synthesis and prevent cell death, as viral DNA replication heavily relies on the host's replication machinery, with only the E1 helicase being an exception. Eventually, the viral genome is encapsidated, and mature virions are released from the superficial epithelial layers. Although these virions are strongly immunogenic, their epithelial location enables them to largely escape immune detection. Additionally, E6 and E7 proteins contribute to persistent asymptomatic infection by interfering with the interferon regulatory factor (IRF), a key component of the host's antiviral immune defense [22].

High-Risk HPV and Cancer: The Functions of E6 and E7

The malignant transformation of normal epithelial cells into cancerous ones is primarily driven by the oncogenic activities of the E6 and E7 proteins, which are encoded by high-risk HPV genotypes. These viral oncoproteins initiate carcinogenesis by targeting and inactivating the key tumor suppressor proteins p53 and retinoblastoma protein (pRB) [23]. Both p53 and pRB serve essential functions in maintaining genomic stability and regulating the cell cycle, effectively preventing uncontrolled cell proliferation. Disruption of their activity by E6 and E7 leads to a cascade of oncogenic events, including genomic instability, suppression of apoptosis, and unregulated cell division, all of which contribute to tumorigenesis [24]. More specifically, E7 protein interferes with pRB by preventing it from binding to the E2F transcription factor, which normally ensures that cells do not enter S-phase prematurely. By binding to pRB, E7 releases E2F, thereby promoting unscheduled progression through the cell cycle and hyperproliferation [10]. During chronic HPV infection, where the immune response fails to clear the virus, the viral replication cycle is altered. This disruption leads to sustained and elevated expression of E6 and E7, further accelerating the process of malignant transformation [25]. Although the inactivation of p53 and pRB is a well-established mechanism, current research indicates that E6 and E7 exert a wider range of oncogenic effects, including the immortalization of epithelial cells and the acquisition of tumor-promoting traits [26]. Emerging data also highlight their role in epigenetic reprogramming during the early phases of cervical neoplasia, positioning these changes as potential biomarkers for early detection of cervical cancer [22].

The Human Microbiome and Its Impact on Cervical Cancer

The human microbiome comprises a remarkably diverse and dynamic community of bacteria, viruses, protozoa, and fungi, forming an ecological system that is even more complex than the human genome itself. It is essential for numerous bodily functions, including immune system development, fighting pathogens, nutrient absorption, vitamin synthesis, fat storage, and potentially influencing behaviour [27]. However, this fragile equilibrium may be altered by a range of factors, including acute diarrheal illnesses, antibiotic administration, individual physiological characteristics, and even dietary habits [28]. The cervicovaginal microbiome is remarkably diverse, harbouring between 20 and 140 different bacterial species within each individual, with significant variations observed over time and between people [29]. Interestingly, some researchers propose that vaginal inflammation is frequently driven not by the introduction of external pathogens, but by disruptions in the composition and abundance of the native vaginal microbiota—a condition referred to as dysbiosis [30]. Research on the cervicovaginal microbiome has revealed intriguing connections between bacterial communities, HPV infection, and the onset of cervical cancer. These findings suggest that specific microorganisms or the environment they create within the cervicovaginal tract may play a role in CC progression [31]. Beyond bacteria, the presence of fungal communities has also been observed. The fungus *Candida albicans*, for example, constitutes over 70% of vaginal fungi and can behave as an opportunistic pathogen under certain circumstances. The composition of the cervicovaginal microbiome varies significantly among different ethnic groups [32].

Unveiling the Cervicovaginal Microbiome: Composition and Potential Roles

In 2011, Ravel introduced the concept of "community state types" (CSTs) to categorise vaginal microbial communities based on their dominant bacterial species. These community state types (CSTs) are classified as CST I through V, with each dominated by a specific Lactobacillus species: L. crispatus (CST I), L. gasseri (CST II), L. iners (CST III), and L. jensenii (CST V). In contrast, CST IV is characterized by reduced Lactobacillus dominance and greater microbial diversity, with a predominance of anaerobic bacteria such as Atopobium, Gardnerella, Megasphaera, and Prevotella [12]. Unlike other mucosal surfaces in the body, the cervicovaginal microbiome in most women exhibits remarkable stability and low diversity [33]. The dominant genus within the cervicovaginal microbiome is *Lactobacillus*. These bacteria generate lactic acid, which is essential for sustaining a healthy vaginal environment. The lactic acid produced by

Lactobacillus reduces the vaginal pH to below 4.5, establishing an acidic environment on the mucosal surface. This acidic environment may influence the activity of natural killer cells, potentially reducing their cytotoxicity. Additionally, *Lactobacillus* produces bacteriocins, which possess antibacterial properties. A growing body of research highlights the crucial role of the vaginal microbiota, particularly *Lactobacillus* species, in safeguarding both the reproductive and gastrointestinal tracts against opportunistic infections [34, 35].

Estrogen and progesterone fluctuations throughout a fertile woman's cycle induce cyclical changes in the vaginal epithelium. This process, involving

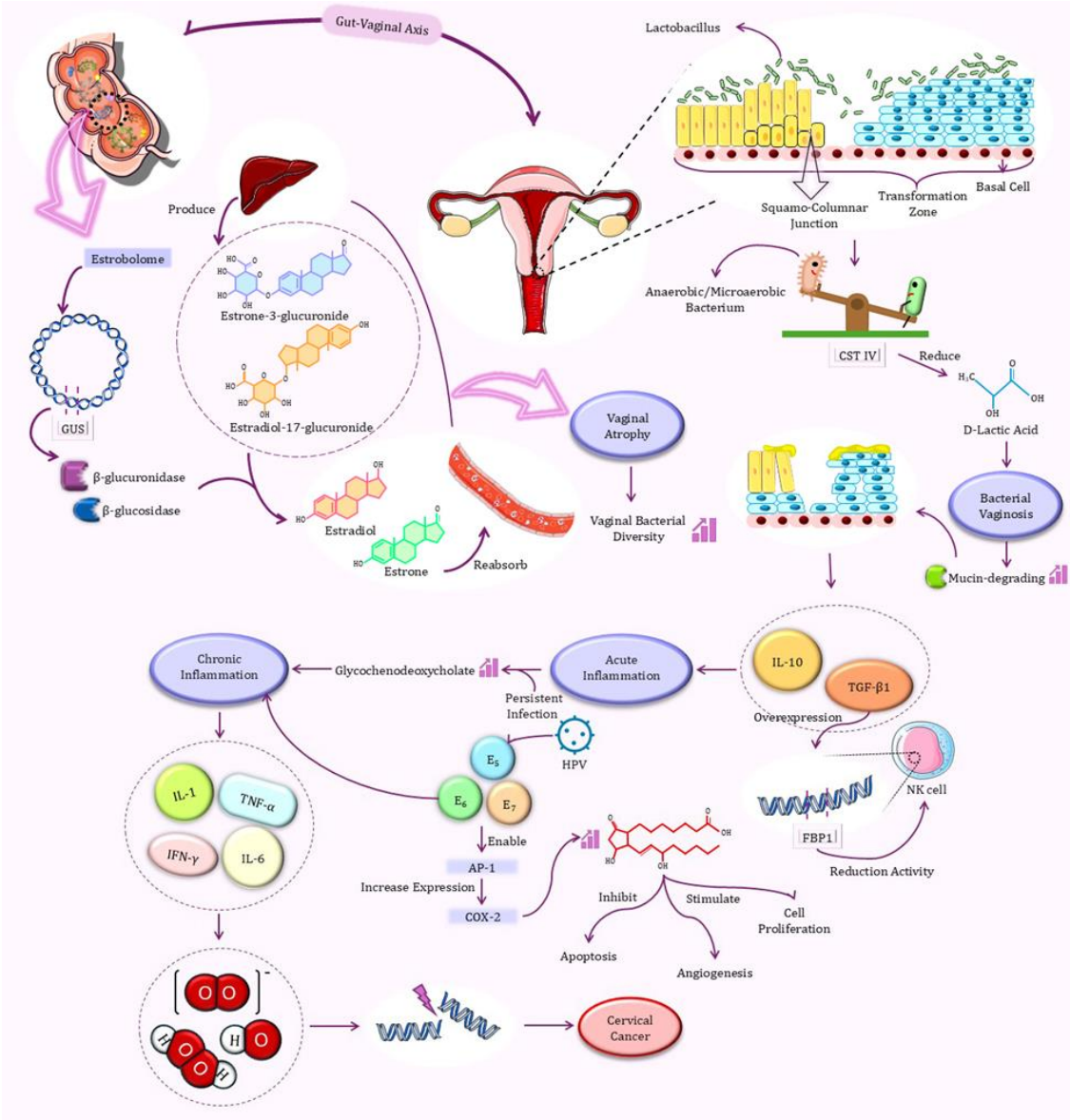


Fig. 2. The astrobleme in the gut microbiome produces β-glucuronidase and β-glucosidase, converting conjugated estrogens into active forms. These active estrogens are reabsorbed into the bloodstream and return to the liver, decreasing estrogen levels. This decline may result in vaginal atrophy and a shift toward greater microbial diversity in the cervical environment, characterized by a reduction in *Lactobacillus* populations and an overrepresentation of anaerobic bacteria, as seen in Community State Type IV (CST IV). Such microbial alterations are associated with an elevated risk of bacterial vaginosis (BV). BV results in more mucin-degrading enzymes, weakening the vaginal and cervical mucus barriers and increasing pro-inflammatory cytokines, leading to acute inflammation. TGF-β promotes the expression of FBP1 in natural killer (NK) cells, reducing their activity and aiding immune evasion. Chronic inflammation, along with persistent HPV infection, raises glycochenodeoxycholate (GCDC) levels, producing reactive oxygen species that damage DNA and may cause cervical cancer. HPV oncoproteins (E_5, E_6, and E_7) activate AP-1, increasing COX-2 and prostaglandin levels, which may stimulate cell proliferation and angiogenesis and inhibit apoptosis, contributing to cancer progression [46, 47].

hyperplasia, desquamation, and repair of vaginal epithelial cells (VECs), generates glycogen that fuels the growth of *Lactobacillus* bacteria. These adsorbed *Lactobacillus* species colonise the VECs, thereby hindering attachment and potential colonisation of pathogenic bacteria that could contribute to tumour formation [36]. Furthermore, *Lactobacillus* has been shown to suppress malignant tumour development by releasing phosphorylated polysaccharides, exopolysaccharides, and peptidoglycans [37].

Among the various isomers of lactic acid (L- and D-lactic acid) produced by certain Lactobacillus strains, D-lactic acid seems particularly effective in preventing vaginal dysbiosis. In addition to lactic acid, Lactobacillus species can synthesise antibacterial peptides like bacteriocins and biosurfactants, further enhancing their protective role [38]. In animal studies, various Lactobacillus strains have been observed to stimulate the production of both pro-inflammatory cytokines (such as IL-1 and IL-6) and anti-inflammatory cytokines (including IL-10 and IL-12), suggesting their potential role in modulating the immune response [39]. Notably, *Lactobacillus* species produce a range of postbiotic metabolites that exhibit beneficial biological activities, including antibiofilm formation, antioxidant properties, pathogen suppression, and immune system modulation. Specifically, certain vaginal Lactobacillus strains, including *L. crispatus*, *L. rhamnosus*, and *L. gasseri*, have exhibited cytotoxic effects on cervical cancer cells while sparing healthy cells [40].

A robust cervicovaginal microbiome protects against urogenital disorders, urinary tract infections, and sexually transmitted infections. It serves as the human body's initial line of defence against these pathogenic entities [41]. Recent advances in microbiome research have pointed to a potential association between the composition of the vaginal microbiota and a woman's susceptibility to HPV infection and subsequent neoplastic transformation [42]. In particular, a decline in *Lactobacillus* species—accompanied by an overgrowth of anaerobic bacteria as observed in bacterial vaginosis (BV)—has been correlated with an increased risk of both acquiring and maintaining HPV infection. BV is a polymicrobial condition characterized by an excessive proliferation of organisms such as *Mycoplasma hominis*, *Gardnerella vaginalis*, and *Mobiluncus* spp., alongside a marked reduction in *Lactobacillus* dominance. Persistent HPV infection, in turn, is a well-established risk factor for the development of cervical intraepithelial neoplasia (CIN), a precancerous lesion of the cervix [43]. Emerging evidence suggests a link, with BV potentially increasing CC and HPV infection rates as well as delaying viral clearance. A diverse microbiome depleted of *Lactobacillus* may contribute to this process [44]. Moreover, microtrauma caused by HPV infection can disrupt the local vaginal immune microenvironment's biological barrier, creating an environment conducive to the growth of aberrant microbiota. This regional microecological imbalance may further promote the upregulation of HPV protein expression, potentially accelerating disease progression [45]. Gut microbiome changes and lower estrogen may cause vaginal dysbiosis—fewer Lactobacillus and more anaerobic bacteria—increasing BV risk. BV-related inflammation and barrier disruption, combined with persistent HPV, may drive oxidative DNA damage and immune evasion. HPV oncoproteins also boost COX-2/prostaglandin signaling, promoting cell growth, angiogenesis, and reduced apoptosis, contributing to cervical cancer [46, 47] (Fig. 2).

Detecting Cervical Cancer: A Range of Screening Options

Several tests are available to screen women for CC and precancer. Each screening test has distinct advantages and disadvantages, and the selection of the most suitable test depends on the facilities available in the community [48].

Cytology-Based Screening for Cervical Cancer: Strengths and Limitations

For decades, cytology-based screening, particularly the Pap smear, has served as a fundamental tool in the prevention of cervical cancer. However, recent European guidelines have shifted preference toward primary HPV-based screening, citing multiple advantages. These benefits include greater sensitivity and diagnostic accuracy, reduced interobserver variability, improved reproducibility, the possibility of self-sampling, and the feasibility of implementing longer screening intervals [49]. Types of cytology-based screening are as follows:

Conventional Pap Smear (CPS) Test

The traditional Pap smear involves the collection of cervical cells from the transformation zone of the cervix and their transfer onto a glass slide. This approach demonstrates moderate sensitivity (approximately 55–65%) and specificity (around 65–75%) in detecting precancerous cervical lesions. However, improvements in sample preparation methods could enhance its diagnostic performance and further reduce cervical cancer incidence [50].

Liquid-Based Cytology (LBC) Pap Test

LBC, introduced in the mid-1990s, utilizes a liquid medium for processing cervical samples. LBC offers several advantages over conventional methods, such as fewer unsatisfactory results, more representative cell collection, uniform distribution of cells, and the possibility of utilizing residual material for HPV testing. Additionally, it allows for shorter screening times and may improve the detection rates of high-

grade squamous intraepithelial lesions (HSIL) [51].

Aiding Pap Smear Analysis: The Rise of Computer Assistance

Since the 1960s, researchers have explored the development of computer-assisted Pap smear analysis systems. These efforts culminated in the approval of several systems by the U.S. Food and Drug Administration (FDA) since 1998, including the AutoPap 300 and PapNet. Automation has also been applied to various aspects of Pap smear interpretation. One of the earliest examples was the Cytoanalyzer, developed in the United States, which used features such as nuclear size and optical density to automate cell screening—marking a significant early step in the integration of artificial intelligence into cytological diagnostics [52]. AutoCyte Screen represents a semi-automated approach where a human reviewer evaluates numerous cell images and decides if a manual review is necessary based on a computer-generated rating. A final diagnosis "within normal limits" is reached if both reviewer and computer agree, signifying no further action is needed. Conversely, cases flagged by either the cytologist or the computer prompt a manual evaluation [48]. (Table 1) summarizes key techniques for automated and semi-automated detection and classification of cervical cancer from Pap smear images, underscoring the continuous technological evolution in this area.

Table 1. Automated Detection and Classification Methods for Cervical Cancer in Pap Smear Images

Datasets	Pre-processing	Segmentation	Classification	Features	Results	Paper	References
Herlev University Medical Center	Contrast boosting	Neural networks	LMAM and OLMAM algorithms	20 morphological features	Classification accuracy of 98.86% was achieved	Enhanced Pap Smear Cytology Analysis Using a Second-Order Neural Network	[53]
Fortis Hospital in India single-cell data sets	Gaussian filter and histogram equalization	Preprocessing and Feature Extraction Using Min-Max Scaling and Edge Detection	K-nearest neighborhood	7 morphological features	Using five-fold cross-validation, the classification model achieved an accuracy of 82.9%, reflecting consistent results across folds.	Cervical Cancer Risk Classification Based on Clinical Data Using KNN	[54]
Herlev dataset	Median filter	Patch-based fuzzy C-means and FCM	Fuzzy C-means	Morphological features	Accuracies of 93.78% and 99.27% for 7 and 2-class classification	Automated Cervical Cell Detection and Classification in Pap Smear Cytology	[55]
Histology image dataset (histology DS2828)	A Robust Method for Contrast Enhancement: Contrast-Limited Adaptive Histogram Equalization	K-means segmentation algorithm	-NN, fuzzy KNN, SVM and random forest-based classifier	125 Nucleus and cytoplasm morphologic features	Accuracy, specificity and sensitivity of 92%, 94% and 81%	Clinically-Informed Detection and Classification of Cancer from Biopsy Microscopy Data	[56]
Liquid-based cytology slides	Image Enhancement Using Histogram Equalization and Median Filtering	Adaptive threshold	C4.5 and Logical Regression classifier	20 Morphological and 8 texture features	Recognition rates of 95.6% achieved	Automated Cervical Cell Detection via a Hierarchical Cascade Classifier	[57]
Image	Image Segmentation Based on Adaptive Histogram Equalization and Otsu's Threshold Selection	Chaos theory corresponds to R, G and B value	Pixel-level classification and shape analysis	Morphometric, densitometry, colorimetric and textural feature	Preserves the color of the images and data loss is minimal	Fuzzy clustering-based image segmentation of pap smear images of cervical cancer cells using the FCM algorithm	[58]

HPV DNA Testing: A Promising Tool for Cervical Cancer Screening

The connection between specific high-risk strains of HPV and the onset of cervical cancer has sparked interest in utilising HPV DNA testing for screening purposes. The capability of these sensitive tests to detect carcinogenic HPV types carries significant implications. Clinical guidelines currently advocate for HPV testing in women with ambiguous Pap smear results, highlighting its potential for more accurate screening [59]. Non-randomized studies and reviews suggest that HPV DNA testing may surpass Pap tests in sensitivity when identifying precancerous lesions and cervical cancer during population screening. While HPV DNA testing offers advantages, its use has limitations. Despite evidence for higher sensitivity, HPV testing is only approved in the US as an adjunct to Pap cytology, not a replacement. Randomised controlled trials comparing them directly are still lacking [60]. One benefit of HPV DNA testing is its objective result, potentially simplifying implementation in resource-limited settings. The question of whether HPV DNA testing should serve as the primary screening method instead of Pap cytology remains a topic of debate. Factors such as implementation challenges, cost-effectiveness, and algorithmic considerations differ across countries [61].

A Promising Approach for Resource-Limited Settings: Visual Inspection with Acetic Acid (VIA)

Visual inspection with acetic acid (VIA) has emerged as a promising CC screening technique for areas with limited healthcare resources. VIA is a simple and cost-effective method performed by a qualified healthcare professional, in which a 3-5% acetic acid solution is applied to the cervix for 1-2 minutes. The healthcare provider then examines the transformation zone for the presence of acetowhite epithelium, a sign of potentially abnormal cellular changes [62]. VIA offers several advantages for resource-limited settings, including affordability, simplicity, lack of infrastructure, ease of usage (paramedical staff can perform it), high sensitivity, and rapid resultsIn addition to VIA, other visual tests are utilized for cervical cancer screening, including naked-eye examination without acetic acid (downstaging), visual inspection with Lugol's iodine (VILI), and VIAM (VIA with magnification devices) [63].

Colposcopy: A Closer Look for Diagnosis

A colposcopy is a crucial diagnostic tool following an abnormal CC screening test. This procedure involves using a colposcope, a magnifying instrument, to examine the cervix in detail, typically at up to 30 times magnification. During colposcopy, the healthcare provider focuses on the transition zone and the squamocolumnar junction (SCJ). Colposcopy-guided cervical biopsy remains the gold standard for diagnosing precancerous and malignant cervical lesions. Numerous studies have confirmed that colposcopy has played a significant role in decreasing both the incidence and mortality associated with cervical cancer [64].

Broadening the Treatment Landscape for Cervical Cancer

Despite these advancements, cervical cancer (CC) continues to impose a substantial health burden, particularly in low-resource settings, where diagnosis often occurs at advanced stages. Fortunately, molecular insights into cervical carcinogenesis have paved the way for innovative therapeutic strategies, such as anti-angiogenic agents, immune checkpoint inhibitors, therapeutic vaccines, and nanotechnology-based treatments [65]. The major treatment modalities currently used or under investigation for CC are summarized in Table 2.

Anti-angiogenic treatment

Angiogenesis, or the formation of new blood vessels, is a critical factor in tumor growth and metastasis, and cervical cancer is no exception. Research has identified several pro-angiogenic factors involved in this process, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [66]. Anti-angiogenic drugs aim to starve tumours by hindering new blood vessel formation. Two main categories of these drugs are used in gynaecological cancers: single-pathway and multiple-pathway inhibitors. Single-pathway inhibitors target specific molecules involved in angiogenesis. For example, monoclonal antibodies like bevacizumab and chimeric soluble receptors like aflibercept block VEGF from binding to its receptors, effectively halting its growth-promoting effects [67].

Research suggests a unique relationship between specific isoforms of VEGF and CC development. In uterine CC, VEGF165 and VEGF121 isoforms are the dominant types. Interestingly, these isoforms are found at significantly higher levels in some late-stage adenocarcinomas compared to squamous cell carcinomas and other adenocarcinoma cases. This observation leads to a potential explanation: the elevated levels of VEGF165 and VEGF121 in advanced adenocarcinomas might be associated with their slower progression. The increased angiogenic activity of these isoforms could create a more controlled growth pattern than other CC types. Studies also highlight a possible connection between VEGF and COX-2, another factor involved in angiogenesis. This link suggests that long-term use of COX-2 inhibitors

after treatment for advanced CC might be a strategy to explore. By potentially suppressing VEGF activity, these drugs could help prevent tumour regrowth or recurrence [68].

Immune checkpoint inhibitors

Recent breakthroughs in harnessing the immune system against cancer have ushered in a new era of cancer treatment. Immunotherapy leverages two main strategies to achieve this: active and passive approaches. Active immunotherapy represents another promising approach, using cancer vaccines to stimulate the host immune system to recognize and destroy malignant cells. Conversely, passive

Table 2. Types of treatment methods for CC.

Drugs or active substances	Nanoparticle type and composition	Major outcomes	References
Antisense oligodeoxynucleotides (AS-ODNs)	lipid-based AS-ODNs	Further studies are still required.	[78]
E6-E7mRNA and E7 protein using siRNAE6 or siRNAE7	siRNAE7-DOPC-NPs	Antitumor activity of siRNA-DOPC-NP	[79]
E6 and E7 antigens	siRNA of HPV 16 E6 was synthesized and transfected into CaSki cells by liposome	The HPV 16 E6 gene interferes and does so specifically and quite effectively.	[80]
Docetaxel	Colic acid-PLGA-b-Vitamin E TPGS copolymer	–	[81]
Bleomycin sulfate	Nanostructured lipid particles	Cervical cancer cells	[82]
Hexylaminolevulinate (HAL)	Bioadhesive pellets of Carbopol 934	Cervical cancer cells	[83]
Peptide antigen derived from E7 oncoprotein of HPV type 16	DOTAP/E7 complex	Antigen-specific anti-cancer activity.	[84]
E6-derived peptide (E6 66–74) and E7	HPV16E6and E7 gene plasmid containing oligomannose liposomes (OML-HPV)	E6 66–74, a peptide derived from E6, can be a target for immunotherapy of cervical cancer.	[85]
Docetaxel	Poly(lactide-co-glycolide) and pluronic F68	Cervical cancer cells	[86]
INF-α	Biphasic vesicles	Biphasic vesicles such as INF-α delivery System can deliver significant levels of INF-α through intact skin and promote therapeutic effects in patients.	[87]
(si)RNA duplexes or small-hairpin (sh)RNA-expressing plasmids targeting the E7 genes of HPV-6b or HPV-11	Cationic liposomes	iRNA specifically modulates the expression of genes for HPV-6b/11 E7, being a useful method to control the condyloma acuminatum.	[88]
Cationic liposomes DOTAP/Cholesterol/DOPE 1/0.75/0.5 (N/P 2.5) with or without 50% DSPE-PEG2000	E6 siRNA complexed with pegylated lipoplexes	Lipoplexes pegylated anti-E6, in the release of cytoplasmic siRNA has demonstrated its	[89]
Docetaxel	D-α-tocopheryl polyethylene glycol 1000 succinate-b-poly(ε-caprolactone-ran-lactide) nanoparticles	Xenograft BALB/c nude mice tumor model	[90]
iRNA	Agarose/liposome/siRNA formulation	Successful topical gel-based delivery of inducers of RNAi to human epithelial cancer cells	[91]
E6 and E7	Liposomal transfection of HPV16E7 siRNA	HPV16 E7, in cases of cervical cancer, may become a new target for gene therapy.	[92]
E7 antigens	LPD (liposome-polycation-DNA)	Regressions of a model cervical cancer tumor; Potent vaccine carrier and/or adjuvant for many antigens.	[93]
Paclitaxel	Paclitaxel-loaded nanoparticles	MCF-7 and HeLa cells	[94]
Cholesterol-conjugated mannan	Liposome-protamine-DNA (LPD) NPs	Enhanced anti-tumor activity	[95]
Docetaxel	D-α-tocopheryl polyethylene glycol 1000 succinate-b-poly (ε-caprolactone-ran-lactide) nanoparticles	Xenograft BALB/c nude mice tumor model	[96]
Silver nanoparticles	Polyethylene glycol	HeLa and CaSki cells	[97]

immunotherapy relies on the direct introduction of exogenous immune-modulating agents, such as immune checkpoint inhibitors (ICIs) or adoptive T-cell therapy (ACT) [69].

Immune checkpoints are crucial physiological mechanisms that prevent the immune system from attacking healthy tissues (autoimmunity). B and T lymphocytes express a transmembrane protein known as programmed cell death protein 1 (PD-1) on their surface. PD-1 interacts with its ligand, PD-L1, and is expressed in cancer cells and antigen-presenting cells (APCs), such as dendritic cells [70]. The peripheral compartment checkpoint, PD-1, regulates how effector T lymphocytes are activated. The binding of PD-L1 to PD-1 triggers an inhibitory signal that prevents further T-cell activation. In this context, the PD-1/PD-L1 immune checkpoint pathway plays a key immunosuppressive role by inhibiting T-cell activity during chronic antigen exposure. Interaction between PD-L1 and CD80 on activated T cells contributes to cytotoxic T-cell downregulation and T-cell exhaustion [71].

Atezolizumab, a fully humanised IgG1 monoclonal antibody, stands out as the first approved drug for checkpoint blockade therapy targeting the PD-L1 protein. Subsequently, other fully human IgG1 monoclonal antibodies, nivolumab and durvalumab, were also authorised as PD-L1 inhibitors. As of March 2019, the FDA recognizes seven ICIs, including ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and cemiplimab [72].

Therapeutic vaccines

Gardasil and Cervarix, the currently available HPV vaccines, offer robust prevention against HPV infection. However, they are not intended for individuals already carrying the virus, and their efficacy is limited to HPV-naive individuals, typically females between 9 and 26 years old. This necessitates the development of therapeutic vaccines aimed at the existing HPV-infected population. Building upon existing HPV vaccines, the nonavalent formulation offers broader protection against CC. This new vaccine targets five additional carcinogenic HPV types (HPV31, HPV33, HPV45, HPV52, and HPV58), potentially increasing the theoretical prevention rate of CC to over 90%. To prevent cervical cancer, current HPV vaccines, including the nonavalent formulation, primarily target HPV types 16 and 18, which account for over 70% of cervical cancer cases [73]. In recent years, peptide-based subunit vaccines have emerged as a promising alternative for the prevention and treatment of various infections and cancers. Unlike traditional whole-cell or protein vaccines, non-redundant peptide vaccines are non-toxic, non-infectious, and are associated with a lower risk of allergic or autoimmune responses [74].

Nano-based treatments

Traditional treatment modalities such as surgery and chemotherapy, although widely used, are often limited by severe adverse effects and the development of drug resistance. While developing safer ICIs offers promise, their overall clinical response rates remain modest. These limitations underscore the urgent need for novel anticancer therapies with improved efficacy and reduced adverse effects [75]. In this context, the low therapeutic index of conventional anticancer drugs and the challenges of delivering them to solid tumours have spurred a growing interest in nano-based drug delivery systems over the past two decades [75]. The European Medicines Agency (EMA) and the U.S. FDA have primarily approved lipid- and protein-based drug delivery systems (DDS) as nanomedicines for cancer treatment. Advancements in liposome technology, along with the incorporation of micelles, polymeric nanomaterials, and inorganic-based nanoparticles, are paving the way for a new generation of nanopharmaceuticals. These novel agents are presently being investigated in clinical trials as standalone therapies or in conjunction with conventional treatments [76]. Nanoscale approaches to drug delivery present several compelling advantages for cancer treatment compared to traditional methods. In contrast, nanotechnology-based therapies offer several advantages, including greater targeting specificity, reduced systemic toxicity, improved bioavailability, and protection of therapeutic agents from chemical and biological degradation.Furthermore, nanoparticles can be designed to release medication at a controlled rate and within a specified timeframe. Additionally, controlled drug release systems help maintain stable therapeutic levels and reduce dosing frequency, thereby enhancing patient compliance and overall treatment efficacy [77].

Conclusions

Recent studies underscore the complex and dynamic nature of the cervicovaginal microbiome. Persistent infection with high-risk HPV (hrHPV) types remains a well-established etiological factor in the development of cervical cancer (CC) as well as vaginal and vulvar malignancies. Meanwhile, emerging evidence suggests that certain bacterial species within the cervicovaginal ecosystem may exert a protective influence against carcinogenesis. These bacteria could potentially prevent HPV infection or aid in viral clearance. Conversely, other bacterial species might contribute to disease development. Therefore, a deeper understanding of how HPV infection influences the cervicovaginal microbiome could be

crucial for predicting the outcomes of HPV infections. Recent advancements in CC treatment, such as anti-angiogenic therapies, immune checkpoint inhibitors, therapeutic vaccines, and non-based delivery systems, represent significant progress in the domain of oncology. These innovative strategies offer more targeted treatment, reduce side effects, address resistance to traditional therapies, and enhance patient outcomes. As research in this field advances, such insights may contribute to the development of more effective and personalized cancer therapies, potentially transforming the future of oncological care.

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Conflict of Interest

The authors declare no conflict of interest.

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